Chemotherapy Dose Calculation and Administration in Exotic Animal Species

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Abstract

There is little information in the literature regarding the use of chemotherapy to treat cancer in exotic animals. This article provides a historical perspective on the use and utility of the body surface area scheme for dosing chemotherapy in animals. Normogram-based recommendations for arriving at a proper chemotherapy dose for the management of cancer in exotic animals are made. It is realistic to offer treatment for many neoplastic diseases in exotic animal species, as long as the limitations are realized and informed consent of the owner is obtained. Copyright 2005 Elsevier Inc. All rights reserved.

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Administration of a drug to a patient carries with it the implicit assumption that the drug will do something to that patient. There are 2 possible clinical outcomes related to drug delivery. The first of these is therapeutic and desirable, whereas the other is toxic and not desirable. The obvious goal in treating a patient with a drug is to maximize the likelihood of producing a therapeutic response while minimizing the likelihood of producing unacceptable toxicity. The dosing variables available to achieve this goal include the amount of drug delivered and the interval or frequency at which the drug can be given. Under ideal circumstances, these variables are based on sound knowledge of the relationship between the dose, or concentration, of the agent; the likelihood of therapeutic and toxic consequences resulting from its delivery; and the duration of drug effects. Unfortunately, such precise information is lacking for most antineoplastic chemotherapeutic agents. Moreover, it is obvious that not all patients are the same. As a result of genotypic and phenotypic differences, the same dose of drug will produce a range of concentration-versus-time profiles in any given group of patients, with the resulting range of therapeutic and toxic responses corresponding to that pharmacokinetic variability.[1-6]

For drugs that produce therapeutic effects at doses far less than those that cause toxicity, the incentive for precise dosing is far less than for drugs with a narrower therapeutic index. The narrow therapeutic index of most antineoplastic agents has provided great impetus to deliver doses as precisely as possible. One of the practices embedded in dosing of antitumor drugs is dosing by body surface area (BSA), most commonly milligrams per square meter (mg/m^2). BSA is equivalent to the two-dimensional surface area of the skin. It is difficult to measure, and therefore commonly estimated on the basis of formulas that use body weight and body length in the calculation. The most commonly used formula was published by Du Bois and Du Bois in 1916.[7] Obviously, the objective at that time was not to develop a

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Table 1. Five formulas for calculating body surface area (BSA), ranked according to the root-mean-squared-error method of prediction by Wang et al.[3]

Author	BSA formula
Boyd††	$BSA\ (m^2) = Wt(kg)^{0.4838} * Ht(cm)^{0.3} * 0.017827$
Gehan and George†	$BSA\ (m^2) = Wt(kg)^{0.51456} * Ht(cm)^{0.42246} * 0.02350$
Mosteller‡	$BSA\ (m^2) = [Ht(cm) * Wt(kg)/3600]^{1/2}$ or
	$BSA\ (m^2) = [Ht(in) * Wt(lbs)/3131]^{1/2}$
Haycock§	$BSA\ (m^2) = Wt(kg)^{0.5378} * Ht(cm)^{0.3964} * 0.024265$
Du Bois and Du Bois‖	$BSA\ (m^2) = Wt(kg)^{0.425} * Ht(cm)^{0.725} * 0.007184$

††This formula is based on 197 observations.[27]
†This formula is based on direct measurements of 401 individuals.[23]
‡This formula is a simple modification of the equation by Gehan and George.[23,28]
§This formula is based on measurements of 81 individuals, ranging from premature infants to adults.[29]
‖This formula is based on measurements of 9 individuals, one of whom was a child.[7]
**Wang Y, Moss J, and Thisted R: Predictors of body surface area. J Clin Anesth 4:4–10, 1992*

formula to dose anticancer agents, because no such drugs yet existed; Du Bois and Du Bois were working on "clinical calorimetry" (now known as basal metabolic rate). The BSA of mammals correlates with basal metabolic rate. As may be expected in warm-blooded animals, BSA is also proportional to blood volume. But, as Baker and coworkers point out, BSA is not well correlated with glomerular filtration rate.[8,9] BSA is also not associated with liver function.[10] The practice of using BSA in scaling drug doses began with Freireich and coworkers, who quantitatively compared toxicity of anticancer agents in the mouse, rat, hamster, dog, monkey, and human.[11] This introduced the use of BSA in scaling a dose from a mouse or other laboratory animal to an initial starting dose for a phase I study in humans.[12] BSA-based dosing eventually found its way to become the requirement for Food and Drug Administration-approved labeling. Subsequent generations of oncologists also viewed BSA-based dosing as the standard for safe and effective administration of cytotoxic chemotherapy.

What may have been lost in this nearly 40-year-old practice is that the difference in size between mouse and man, or dog and man, is far greater than the variability in size among patients.[10,13-15] As with many practices ingrained in the practice of medicine, mg/m^2 dosing of antitumor drugs has become accepted without questioning the soundness or validity of its underlying assumptions, despite the appearance and availability of newer technologies and theories that would make testing of such assumptions possible.[1-6,16] As analytic chemical instrumentation, pharmacokinetic modeling, and increasingly sophisticated means of assessing molecular and clinical outcomes of drug therapy have been developed, there has been an increasing call to test the validity of the assumptions behind mg/m^2 dosing of antitumor drugs to human and animal species.[3,4,6,16]

Chemotherapy Dosing in Exotics

There is little information in the literature regarding the use of chemotherapy to treat cancer in exotic animals.[17] Much of the literature that does exist relies on extrapolation from the human literature or the treatment of dogs and cats, is presented as case reports, and includes inadequate follow-up information. Many articles describe the toxicity of chemotherapeutic agents in rabbits, rats, and mice, but the drugs were often given to healthy animals and often at doses that were not therapeutic.

Nevertheless, it is still possible to offer treatment for many neoplastic diseases in exotic animal species, as long as the limitations are realized and informed consent of the owner is obtained.[17,18] It is important to understand the basic mechanisms of action, potential toxicities, and personnel protection issues before attempting to treat any patient of any species with chemotherapy. Clients should be made aware that there are no currently approved chemotherapy agents for use in exotic animal species, and that these drugs are being used in an experimental manner for compassionate purposes. This means informing clients that in most cases dosing information is limited, and all potential toxicities are yet to be elucidated. This also means that limited informa-

Table 2. Body surface area dosing in dogs and cats using a modification of the Du Bois and Du Bois formula (m^2 = 10.0 × (weight in grams)$^{2/3}$/10000).[1-7,16]

kg	lb	m^2	kg	lb	m^2
0.50	1.1	0.06	33	72.6	1.03
1	2.2	0.10	34	74.8	1.05
2	4.4	0.15	35	77.0	1.07
3	6.6	0.20	36	79.2	1.09
4	8.8	0.25	37	81.4	1.11
5	11.0	0.29	38	83.6	1.13
6	13.2	0.33	39	85.8	1.15
7	15.4	0.36	40	88.0	1.17
8	17.6	0.40	41	90.2	1.19
9	19.8	0.43	42	92.4	1.21
10	22.0	0.46	43	94.6	1.23
11	24.2	0.49	44	96.8	1.25
12	26.4	0.52	45	99.0	1.26
13	28.6	0.55	46	101.2	1.28
14	30.8	0.58	47	103.4	1.30
15	33.0	0.60	48	105.6	1.32
16	35.2	0.63	49	107.8	1.34
17	37.4	0.66	50	110.0	1.36
18	39.6	0.69	52	112.2	1.41
19	41.8	0.71	54	114.4	1.44
20	44.0	0.74	56	116.6	1.48
21	46.2	0.76	58	118.8	1.51
22	48.4	0.78	60	121.0	1.55
23	50.6	0.81	62	123.2	1.58
24	52.8	0.83	64	125.4	1.62
25	55.0	0.85	66	127.6	1.65
26	57.2	0.88	68	129.8	1.68
27	59.4	0.90	70	132.0	1.72
28	61.6	0.92	72	134.2	1.75
29	63.8	0.94	74	136.4	1.78
30	66.0	0.96	76	138.6	1.81
31	68.2	0.99	78	140.8	1.84
32	70.4	1.01	80	143.0	1.88

tion is available with regard to prognosis in most cases.

Only doxorubicin and the platinum-containing chemotherapeutic agents (carboplatin, cisplatin) have been studied in veterinary medicine to determine if dosing by BSA would reduce interpatient variability and toxicoses, and none of these drugs was found to have significant relationships between their pharmacokinetics and BSA.[1-6,16,19,20] Results to date suggest that veterinary BSA estimates may be inaccurate, because the values for

Table 3. Representative surface area to weight ratios (Km) for various species.[11]

Species	Body weight (kg)	Surface area (m^2)	Km factor
Mouse	0.02	0.0066	3.0
Rat	0.15	0.025	5.9
Monkey	3.0	0.24	12
Dog	8.0	0.4	20
Human, child	20	0.8	25
Human, adult	60	1.6	37

Example: To express a mg/kg dose in any given species as the equivalent mg/m^2 dose, multiply the dose by the appropriate Km factor. In the adult human, 100 mg/kg is equivalent to 100 mg/kg × 37 kg/m^2 = 3700 mg/m^2.

the constant (K) and exponent (a) in the formula (BSA = K*W^a) are incorrect or because a linear parameter such as body length is lacking from the formula. Results also suggest that BSA and the physiologic or pharmacologic factors that influence drug exposure may not be closely correlated.[1,2] To illustrate the problem with BSA dosing in dogs, a 30-kg (66-lb) dog has a BSA of 1 m^2. If this dog were to be given doxorubicin at the recommended dosage of 30 mg/m^2, this dog would be given a 30-mg total delivered dose, or 1 mg/kg. However, a 5-kg (11-lb) dog has a BSA of 0.30 m^2 and would be given a dosage of 9 mg (30 mg/m^2 times 0.30 m^2) or 1.8 mg/kg (9 mg divided by 5 kg). This represents an 80% increase in dosage of

Table 4. Equivalent surface area dosage conversion factors.[11]

	To				
From	Mouse	Rat	Monkey	Dog	Man
Mouse	1	¼	¼	¼	1/12
Rat	2	1	½		1/7
Monkey	4	2	1	⅗	⅓
Dog	6	4	⅗	1	½
Man	12	7	3	2	1

Example: Given a dose of 50 mg/kg in the mouse, the appropriate dose in the monkey, assuming equivalency on the basis of mg/m^2, is 50 mg/kg × ¼ = 13 mg/kg.
This table gives approximate factors for converting doses expressed in terms of mg/kg from 1 species to an equivalent surface area dose expressed as mg/kg in the other species tabulated. The assumptions and constants of the formula by Freirich et al. (1966) are used.

Table 5. Chemotherapy agents and dosing recommendations in exotics

Drug	Dose	Tumor type
Ferrets[21,22,26,31-37]		
Vincristine*	0.75 mg/m² i.v.	Lymphoma
	2.0 mg/m² i.v.	Lymphoma
	0.12 mg/kg i.v.	Lymphoma
	0.20 mg/kg i.v.	Lymphoma
Cyclophosphamide†	200 mg/m² p.o., s.c.	Lymphoma
	10 mg/kg p.o.	Lymphoma
L-asparaginase‡	400 IU/kg s.c., i.m.	Lymphoma
Chlorambucil	1 mg/kg p.o.	Lymphoma
Doxorubicin*‡	20 mg/m² i.v.	Lymphoma, squamous cell carcinoma
	2 mg/kg i.v.	Lymphoma
Methotrexate	0.5 mg/kg i.v.	Lymphoma
Bleomycin	10 U/m² s.c.	Squamous cell carcinoma
Avian[5,18,20,24,25,30,38-40]		
Carboplatin	125 mg/m² i.v.	Bile duct carcinoma
	15 mg/kg i.o.	
Chlorambucil	1 mg/kg p.o.	Lymphocytic leukemia, hepatocellular carcinoma
Doxorubicin*‡	60 mg/m² i.v.	Osteosarcoma, hemangiosarcoma
Vincristine*	0.75 mg/m² i.v.	Lymphocytic leukemia
Reptile[18]		
Cytosine arabinoside	30 mg/kg s.c.	Lymphoma (may have caused severe toxicity)
Rodent[18]		
Doxorubicin (liposomal encapsulated)	6 mg/kg i.v.	Mammary adenocarcinoma
Rabbit[41]§		
Carboplatin	150-180 mg/m² i.v. q 3-4 weeks	Carcinoma
CCNU	50 mg/m² p.o. q 3-6 weeks	Lymphoma
Cyclophosphamide†	50 mg/m² p.o. q 24 hours for 2-3 days per week	Lymphoma
	100-200 mg/m² i.v. q 1-3 weeks (often combined with doxorubicin)	Lymphoma
Doxorubicin*‡	1 mg/kg i.v. q 2-3 weeks	Lymphoma
L-asparaginase‡	400 IU/kg i.m. or s.c.	Lymphoma
Mitoxantrone*	5-6 mg/m² i.v. q 3 weeks	Carcinoma
Prednisone	0.5-2.0 mg/kg p.o.	Lymphoma
Vincristine*	0.5-0.7 mg/m² i.v. q 1-2 weeks	Lymphoma

i.m. = intramuscularly, i.v. = intravenously, p.o. = by mouth, s.c. = subcutaneously, i.o. = intraosseous.

**Drug must be administered intravenously via a clean stick to avoid extravasation and perivascular necrosis.*

†Injectable cyclophosphamide can be administered orally at the same dose but may require dilution in propylene glycol for appropriate dosing. Alternately, an oral formulation can be compounded by a professional compounding pharmacy. This drug should be administered in the hospital to avoid unnecessary human contact or risk with the use of a liquid chemotherapeutic.

‡Premedicate with diphenhydramine, 1 to 2 mg/kg, 30 minutes before administration to prevent anaphylactic response.

§Personal observations.

doxorubicin when based on body weight. Doxorubicin clearly does not fit the BSA model, yet studies have not yet been completed to determine the appropriate dosage based on body weight.[3,4] The conclusion, until such studies are conducted in animals of varying body size, shape, weight, and

length, is that chemotherapeutic drug dose selection in human and veterinary medicine remains anecdotal.

Thus, BSA is a difficult concept to define and is a variable that is extremely difficult to measure reproducibly. Several different formulae for predicting surface area in humans from measurements of height and weight have been derived (Table 1). The author prefer to use the modified Du Bois formula[7] (Table 2) for chemotherapy dosing in dogs and cats, and the Freireich formula[11] for scaling up from mouse and rat to other warm-blooded species or exotics (Tables 3 and 4). Despite anatomical, physiological, and biochemical differences among animal species, the pharmacokinetic disposition of many chemotherapy agents in avians,[20] reptiles,[17] ferrets,[21,22] and other exotics is similar in some respects to the kinetics reported previously in dogs[3,6,16] and humans.[23] Thus, it is likely that specific dosing requirements would be largely determined by the sensitivity of the tumor to the chemotherapy agent and by its toxicity, rather than any large-scale dosage alterations driven by significant pharmacokinetic differences. Current recommendations are to dose chemotherapy in avians as recommended in dogs[3,6,16,20,24,25] and to dose chemotherapy in ferrets as recommended for cats[4,5,21,22,26] (Table 5).

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